

EDITORIAL COMMENT

Atrial Natriuretic Peptide for the Prevention of Contrast-Induced Nephropathy

What's Old Is New But at the Right Dose and Duration of Therapy!*

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Contrast-induced nephropathy (CIN) is most commonly defined as a 25% increase in serum creatinine concentration from the baseline value, or an absolute increase of at least 0.5 mg/dl, that appears within 48 h after the administration of radiographic contrast media in the absence of an alternative cause (1). Contrast-induced nephropathy is the third most common cause of new acute renal failure in hospitalized patients (2). The incidence of CIN in the general population has been reported to be 2% to 5%. However, the incidence may be as high as 25% in patients with pre-existing renal impairment or certain risk factors, such as diabetes, congestive heart failure, advanced age, and concurrent administration of nephrotoxic drugs (3). Despite the

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fact that CIN most commonly manifests as a nonoliguric and asymptomatic transient decline in renal function, cohort studies have shown that it is associated with significant morbidity and mortality rates independent of other risk factors. Specifically, Levy et al. (4) reported in a study of more than 16,000 patients undergoing contrast-enhanced examinations that in patients who developed CIN, there was a significantly higher mortality rate than in the patient group from the same population matched for age and baseline creatinine levels who underwent similar contrast-enhanced procedures but did not develop CIN (34% vs.

7%). Thus, CIN was found to result in excessive mortality rates, independent of other risk factors.

Although the exact underlying mechanisms of CIN have yet to be fully elucidated, it is most likely multifactorial because of increased adenosine, endothelin, and free-radical-induced vasoconstriction with decreased local prostaglandin and nitric oxide (NO)-mediated vasodilation resulting in renal medulla ischemia (5). Contrast agents also have direct toxic effects on renal tubular cells, resulting in vacuolization, altered mitochondrial function, and apoptosis (6).

As with all medical conditions, the best treatment for CIN is to prevent it. General measures to minimize the incidence include using the minimal effective dose, eliminating potentially nephrotoxic drugs at least 24 h before the study, and adequate hydration. Several drug interventions, including the use of *N*-acetylcysteine, theophylline, fenoldopam, and other agents have been investigated as preventive strategies in CIN; however, the results have been heterogeneous and are difficult to compare across the different treatment strategies. In a recent meta-analysis by Kelly et al. (7) that included 33 CIN prevention trials involving 3,622 patients, the investigators reported that *N*-acetylcysteine is more renoprotective than hydration alone and theophylline may also reduce risk for contrast-induced nephropathy, although the detected association was not significant. The remaining agents did not significantly affect risk. Importantly, the investigators pointed out that the available studies used in the meta-analysis examined laboratory end points (such as an increase in serum creatinine levels) rather than clinical end points (such as dialysis or death).

In this issue of the *Journal*, Morikawa et al. (8) reported a single-center controlled, randomized trial designed to examine the protective effects of atrial natriuretic peptide (ANP) on CIN after coronary angiography. They randomized 254 consecutive patients with serum creatinine concentrations of ≥ 1.3 mg/dl, where patients received either ANP or lactated Ringer solution alone initiated 4 to 6 h before angiography and continued for 48 h. The investigators reported that the prevalence of CIN, defined as a 25% increase in creatinine or an increase in creatinine of ≥ 0.5 mg/dl from baseline within 48 h, was significantly lower in the ANP group than in the control group (3.2% vs. 11.7%, respectively; $p = 0.015$). Multivariate analysis revealed that the use of >155 ml of contrast medium (odds ratio: 6.89; $p < 0.001$) and ANP treatment (odds ratio: 0.24; $p = 0.016$) were significant predictors of developing CIN. The incidence of an increase in creatinine of $\geq 25\%$ or of ≥ 0.5 mg/dl from baseline at 1 month was also significantly lower in the ANP group than in the control group ($p = 0.006$).

The natriuretic peptides are a group of structurally similar but genetically distinct peptides that have diverse actions in cardiovascular, renal, and endocrine homeostasis. Both ANP and B-type natriuretic peptide (BNP) are of myocardial cell origin, and C-type natriuretic peptide is of endo-

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thelial origin; ANP and BNP bind to the natriuretic peptide-A receptor, which via 3',5'-cyclic guanosine monophosphate (cGMP) mediates natriuresis, vasodilation, enhances glomerular filtration rate (GFR), renin inhibition, and anti-ischemic properties (9). Pre-clinical studies have shown that ANP and BNP, via the natriuretic peptide-A receptor, increases GFR and glomerular hydrostatic pressure by dilating afferent arterioles and constricting efferent arterioles, while blocking tubular reabsorption of sodium and disrupting the tubuloglomerular feedback mechanism (10). Furthermore, they have direct action on the renal mesangial cells to increase glomerular ultrafiltration coefficient, which in turn increases GFR (11). These renal enhancing properties together with anti-ischemic and anti-inflammatory properties have resulted in clinical investigations to determine the therapeutic potential of ANP and BNP for acute renal failure and the prevention of CIN. Despite encouraging experimental data, initial clinical trials with ANP in 2 multicenter, prospective randomized trials in patients with acute tubular necrosis or late oliguric acute renal failure were disappointing (12,13). In these studies, ANP, at a dose of 200 ng/kg/min for 24 h, had no effect on the need for dialysis, the rate of dialysis-free survival at 21 days after treatment, or overall mortality rate. Subsequently, Sward et al. (14) reported in a single-center, randomized, double-blind, placebo-controlled trial that there was a significant reduction of renal impairment, and of the need for dialysis after cardiopulmonary bypass, with the use of long-term infusion (5 days) of recombinant ANP at a dose of 50 ng/kg/min. The 2 main differences that may account for the discrepancies of their results and previous studies are the dose of ANP used and the duration of ANP infusion. The earlier studies used a high dose of ANP at 200 ng/kg/min, whereas Sward et al. (14) used the low dose of 50 ng/kg/min, which was associated with less hypotension as compared with the earlier high-dose studies. Furthermore, in the earlier studies, the infusion duration was only 24 h, whereas Sward et al. (14) infused ANP for 5 days. Similarly, Krunik et al. (15) reported that ANP infusion at 10, 50, and 100 ng/kg/min initiated at 30 min before and continued for 30 min after the angiographic procedure did not reduce the incidence of CIN in patients with chronic renal insufficiency. Comparatively, in the study by Morikawa et al. (8), the investigators infused ANP at 42 ng/kg/min initiated at 4 to 6 h before angiography and continued for 48 h, and showed that it was effective in preventing CIN. More importantly, this strategy also prevented worsening renal function at 1 month. This supports the concept that in addition to the dose, the duration of infusion is an important determinant in the efficacy of ANP in preventing CIN. Hence, Morikawa et al. (8) should be commended for making the effort to review the previous studies and determining the appropriate dose and duration of infusion for their study. Despite the favorable renal enhancing actions of both ANP and BNP, the hypotension associated with higher doses results in decreased renal perfusion pressure, limits the renal enhanc-

ing actions, and may even have detrimental renal effects. This is also shown in the clinical investigations of BNP (nesiritide), in which studies have shown that at the clinical dose or higher (2- μ g/kg bolus followed by continuous infusion of 0.01 μ g/kg/min), there is little renal enhancing action and it may even be associated with worsening renal function (16,17). In contrast, at lower doses (0.01 or 0.005 μ g/kg/min without bolus), there are renal enhancing or preserving properties (18-20).

In summary, CIN is a common cause of hospital-acquired acute renal failure and is associated with increased morbidity and mortality. There is currently no established optimal strategy for the prevention of CIN. The study by Morikawa et al. (8) has shown the potential of administration of ANP to prevent CIN. More importantly, the investigators have carefully determined the effective dose and duration of intervention. A large multiple-center, randomized, placebo-controlled trial that is adequately powered with clinical end points such as reduction in dialysis, hospital stay, etc., is clearly warranted based on the promising results from this pilot study.

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REFERENCES

- Barrett BJ, Parfrey PS. Prevention of nephrotoxicity induced by radioccontrast agents. *N Engl J Med* 1994;331:1449-50.
- Tublin ME, Murphy ME, Tessler FN. Current concepts in contrast media-induced nephropathy. *AJR Am J Roentgenol* 1998;171:933-9.
- Morcos SK, Thomsen HS, Webb JA. Contrast-media-induced nephrotoxicity: a consensus report. Contrast Media Safety Committee, European Society of Urogenital Radiology (ESUR). *Eur Radiol* 1999;9:1602-13.
- Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality. A cohort analysis. *JAMA* 1996;275:1489-94.
- Weisberg LS, Kurnik PB, Kurnik BR. Radiocontrast-induced nephropathy in humans: role of renal vasoconstriction. *Kidney Int* 1992;41:1408-15.
- Persson PB, Hansell P, Liss P. Pathophysiology of contrast medium-induced nephropathy. *Kidney Int* 2005;68:14-22.
- Kelly AM, Dwamena B, Cronin P, Bernstein SJ, Carlos RC. Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. *Ann Intern Med* 2008;148:284-94.
- Morikawa S, Sone T, Tsuboi H, et al. Renal protective effects and the prevention of contrast-induced nephropathy by atrial natriuretic peptide. *J Am Coll Cardiol* 2009;53:1040-6.
- Chen HH, Burnett JC Jr. The natriuretic peptides in heart failure: diagnostic and therapeutic potentials. *Proc Assoc Am Physicians* 1999;111:406-16.
- Margulies KB, Burnett JC Jr. Atrial natriuretic factor modulates whole kidney tubuloglomerular feedback. *Am J Physiol* 1990;259:R97-101.
- Butlen D, Mistouli M, Morel F. Atrial natriuretic peptide receptors along the rat and rabbit nephrons: [125I] alpha-rat atrial natriuretic peptide binding in microdissected glomeruli and tubules. *Pflügers Arch* 1987;408:356-65.
- Allgren RL, Marbury TC, Rahman SN, et al., for the Auriculin Anaritide Acute Renal Failure Study Group. Anaritide in acute tubular necrosis. *N Engl J Med* 1997;336:828-34.
- Lewis J, Salem MM, Chertow GM, et al., for the Anaritide Acute Renal Failure Study Group. Atrial natriuretic factor in oliguric acute renal failure. *Am J Kidney Dis* 2000;36:767-74.

14. Sward K, Valsson F, Odencrants P, Samuelsson O, Ricksten SE. Recombinant human atrial natriuretic peptide in ischemic acute renal failure: a randomized placebo-controlled trial. *Crit Care Med* 2004;32:1310–5.
 15. Kurnik BR, Allgren RL, Genter FC, Solomon RJ, Bates ER, Weisberg LS. Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. *Am J Kidney Dis* 1998;31:674–80.
 16. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation* 2005;111:1487–91.
 17. Wang DJ, Dowling TC, Meadows D, et al. Nesiritide does not improve renal function in patients with chronic heart failure and worsening serum creatinine. *Circulation* 2004;110:1620–5.
 18. Chen HH, Sundt TM, Cook DJ, Heublein DM, Burnett JC Jr. Low dose nesiritide and the preservation of renal function in patients with renal dysfunction undergoing cardiopulmonary-bypass surgery: a double-blind placebo-controlled pilot study. *Circulation* 2007;116:1134–8.
 19. Riter HG, Redfield MM, Burnett JC, Chen HH. Nonhypotensive low-dose nesiritide has differential renal effects compared with standard-dose nesiritide in patients with acute decompensated heart failure and renal dysfunction. *J Am Coll Cardiol* 2006;47:2334–5.
 20. Mentzer RM Jr., Oz MC, Sladen RN, et al. Effects of perioperative nesiritide in patients with left ventricular dysfunction undergoing cardiac surgery: the NAPA trial. *J Am Coll Cardiol* 2007;49:716–26.
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